



MAR 3 1 2011

DATE:**FROM:** Helen Chen, M.D., Investigational Drug Branch, CTEP, DCTD, NCI**SUBJECT:** Bevacizumab (rhuMAb VEGF) NCI IND Safety Report, AE# 1442953**TO:** Investigators Using Bevacizumab (NSC 704865)

The U.S. Food and Drug Administration (FDA) regulations require sponsors of clinical studies conducted under a U.S. IND to notify the FDA and all participating investigators of any serious and unexpected adverse experiences that are possibly related to the investigational agent. Please find attached a copy of an IND Safety Report recently submitted to the FDA for the CTEP-sponsored investigational agent bevacizumab.

The following must be completed by all investigators using bevacizumab under NCI INDs 7921 and 11460.

- Send a copy of this letter to your Institutional Review Board (IRB) of record according to your policies and procedures.
- File a copy of the IND Safety Report in your protocol file.

If your study is not covered under INDs 7921 and 11460, it is strongly recommended that you follow the instructions above.

Please note that for Cooperative Group studies, the Cooperative Group Operations Office will provide instructions for IRB submissions, any patient notifications, etc.

Based on CTEP's assessment of the current information in light of previous experience with bevacizumab, there does not appear to be a change in the risk-benefit ratio for bevacizumab studies; therefore, CTEP is not requiring a protocol amendment at this time.

Please continue to report events according to the adverse event reporting guidelines in your protocol(s).

The attached Adverse Events Assessment describes the adverse event(s) (synopsis provided below), relevant previous experience under these INDs and/or NSC, and the total number of patients enrolled in trials under these INDs and/or NSC.

A 53-year-old male with recurrent squamous cell carcinoma of the head and neck expired suddenly while on a phase 3 study using the investigational agent bevacizumab in combination with docetaxel and cisplatin.

ADVERSE EVENTS ASSESSMENT

IND 7921	ADVERSE EXPERIENCE REPORT NO.
NSC 704865	IND Safety Report: # 1
Bevacizumab (rhuMAb VEGF)	Event: Gr. 5: Death: Death NOS
AE: 1442953	Protocol: E1305

The patient was a 53-year-old male with recurrent squamous cell carcinoma of the head and neck who expired suddenly while on a phase 3 study using the investigational agent bevacizumab in combination with docetaxel and cisplatin. The patient began his first course of treatment on December 16, 2010, receiving bevacizumab 15 mg/kg IV over 30-90 minutes on Day 1, docetaxel 75 mg/m² IV over 1 hr on Day 1, and cisplatin 75 mg/m² IV over 1-2 hrs on Day 1, every 21 days. He received his last doses of bevacizumab, docetaxel, and cisplatin on January 26, 2011 (Cycle 3, Day 1).

The patient was diagnosed with squamous cell carcinoma of the head and neck in March 2006. He was status post right modified radical neck dissection surgery in March 2006, multiple-agent systemic chemotherapy from April to May 2006, and radiation therapy between March and May 2006. He was diagnosed with metastatic disease in November, 2010. Baseline CT scan of the chest with showed posterior left upper lobe and left-based lesion. However, a CT scan of the neck showed no evidence of residual disease in the larynx or neck. A bilateral extra-cranial arterial study revealed antegrade flow in the bilateral vertebral arteries, and bilateral atherosclerotic vascular disease with 50-69% stenosis in right internal carotid artery and no hemodynamically significant stenosis on the left.

The patient began the investigational agent on December 16, 2010. On December 23, 2010 (Cycle 1, Day 8), he presented to the clinic with a 2-day history of itchy and red rash over his torso. The patient had a maculopapular rash over his chest and back without pustules or vesicles. It was felt that he developed an allergic rash presumably secondary to Cipro[®]; although, the possibility of rash as a side effect of docetaxel was also considered. The patient was started on Medrol[®] Dosepak[™].

At a follow-up visit on January 6, 2011 (Cycle 2, Day 1), the patient reported tolerating the investigational therapy extremely well; however, he admitted to experiencing rare but transient tinnitus in his ear. The patient received the investigational treatment as scheduled.

On January 26, 2011 (Cycle 3, Day 1), the patient presented to the clinic for the investigational treatment, and complained of mild tinnitus which lasted about 30 seconds at a time. He reported no change in his hearing function. The patient had a temperature of 98.2 °F, pulse rate of 104 bpm, and a BP of 123/81 mmHg. A CT scan of the chest with contrast showed an overall improvement in the left lung and pleural based lesions as compared to the CT scan of the chest with contrast on December 6, 2010. He received the investigational therapy as planned. The patient was referred for an audiology evaluation in light of his grade 1 tinnitus. Although he was scheduled for an audiology appointment on January 28, 2011, he did not keep this appointment. There is no record to explain why the appointment was not kept.

On February 14, 2011 (Cycle 3, Day 20), the site observed the patient's name in the local newspaper obituary. Further investigation revealed that he was found dead at home alone on February 12, 2011 (Cycle 3, Day 18). On March 10, 2011, the medical examiner reported the patient's cause of death as complications from his cancer chemotherapy.

The patient's past medical history was significant for chronic obstructive pulmonary disease (COPD), and his surgical history was significant for a direct laryngoscopy with biopsies and a percutaneous endoscopic gastrostomy tube placement (both in March 2006), and left intrajugular Port-A-Cath placement in December 2010. His social history was significant for cigarette smoking. Medications taken at the time

of the event included Detrol[®] LA, Spiriva[®], Cipro[®], and Vicodin[®].

There have been 124 other cases of death NOS and 61 other cases of sudden death NOS reported to NCI as serious adverse events through AdEERS under the bevacizumab NSC and/or IND. The attributions are summarized in the following table:


Adverse Event	Grade	Attribution
Death NOS (n = 124)	5	42 Unrelated, 49 Unlikely, 32 Possible, 1 Probable
Sudden death NOS (n = 61)	5	6 Unrelated, 16 Unlikely, 36 Possible, 3 Probable

There have been 31,563 patients enrolled in NCI-sponsored clinical trials under the bevacizumab IND and/or NSC.

In this case, the cause of death is not clear and possibilities could include CNS, cardiac or pulmonary events. Given the temporal relationship of the events, attribution to the investigational therapy cannot be ruled out.

	Death NOS
Bevacizumab (rhuMAb VEGF)	Probable
Cisplatin	Possible
Docetaxel	Possible
Head and neck squamous cell carcinoma	Unrelated
Arthelosclerotic disease	Possible

Date: 2/28/11

Signature: 
 Helen Chen, M.D.
 (IDB Monitor for bevacizumab)

If this assessment is changed, we will notify your office.

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 Genentech, Inc.